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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,462	05/05/2006	Makrina Savvidou	HO-P03236US0	8934

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,462	SAVVIDOU ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/31/07; 1/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims filed August 31, 2007 has been received and entered. Claims 1 has been amended, while claims 3, 12-28 have been canceled. Claims 1-2, 4-10 and 11 are pending.

Election/Restrictions

Applicant's election without traverse of claims 1-2 and 4-11 in the reply filed on August 31, 2007 is acknowledged.

Claims 1-2, 4-10 and 11 are under consideration.

Information Disclosure Statement

The Information Disclosure Statement submitted on 8/31/2007 and 1/11/2006 have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims are directed to a method of identifying whether or not a pregnant woman is at risk of developing pre-eclampsia or whether or not her fetus is at risk of developing IUGR by measuring the asymmetric dimethylarginine (ADMA) in any tissue or fluids of a pregnant woman at a stage of pregnancy from 4-25 weeks gestation and determining whether or not the ADMA is greater than 2.0 μmol/l in the woman. Subsequent claims limit the method of claim 1 to include measurement of ADMA in any fluid sample take from the woman. Claims4 and 5 limit the stage to pregnancy to include 10 to 25 or 15 to 25 weeks of gestation respectively. In addition, claim 6 limits the determination level of ADMA to include ADMA level at least 3 times the normal pregnancy, while claim 7 include determination of

ADMA/SDMA ration that is greater then normal pregnancy ration subsequently limiting to at least 5 times more then normal pregnancy ratio.

It is noted that as instantly recited, claimed invention reads on measuring ADMA levels in a pregnant woman at 4 to 25 weeks gestation in any tissue of sample to diagnose pre-eclampsia or fetus being at risk of developing IUGR. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in any tissue or fluid sample taken from the woman (ii) how presence of elevated level of ADMA will be a specific method for identifying the susceptibility of the woman developing pre-eclampsia or fetus developing of IUGR. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of diagnosing complex disease like pre-eclampsia or IUGR by measuring the level of ADMA will not be specific and is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced. As will be shown below, broad aspects were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

As a first issue, the claims embrace a method of identifying whether or not a pregnant woman is at risk of developing pre-eclampsia or whether or not her fetus is at risk of developing intrauterine growth restriction (IUGR) by measuring asymmetric dimethylarginine (ADMA) levels in the any tissue or body fluid of a pregnant woman (4-25 week of gestation). The specification contemplated increased plasma level of ADMA associated with increased susceptibility to or risk of developing of pre-eclampsia or increased susceptibility to or risk of developing of IUGR is typically greater than about 2.0 μmol/L. (see page 4, lines 20-25). The

specification teaches women with bilateral notches had significantly higher levels of ADMA compared to the women with normal uterine artery Doppler waveforms (2.4 μmol/L vs. 0.81 μmol/L respectively, Figure 2, page 21). It is also noted that specification discloses that women who subsequently developed pre-eclampsia had significantly higher levels of ADMA compared to the women who had normal pregnancies (Table 3). Prior to instant invention, The state of art effectively summarized by the references of Cooke (Circulation. 2004 Apr 20;109(15):1813-8) disclose that level of asymmetric dimethylarginine (ADMA) also correlates well with traditional and non-traditional cardiovascular risk factors. The art teaches that ADMA is a strong predictor of cardiovascular events and death in selected patient populations (Kielstein et al Am J Kidney Dis. 2005; 46: 186–202) and a marker of progression of various chronic renal diseases. It is noted that high ADMA levels have been associated with alterations in the regulation of cerebral blood flow and neural function, with insulin resistance, thyroid dysfunction, and alterations in bone homeostasis, fertility, and erectile function (see abstract Kielstein et al Am J Kidney Dis. 2005; 46: 186–202). In addition, higher levels of ADMA in plasma is also observed in a number of other conditions including onset of menopause, smoking, infection high salt intake and fatty food intake (see Fang et al Hypertension 2006; 48: 724-729; Fard et al, Arterioscler Thromb Vasc Biol 2000; 20: 2039-2044 and Hamasaki et al Gen Pharmacol 1997; 28: 653-659). Therefore, it is evident from the teaching of the cited references that ADMA could be modulated in other disorders and conditions in pregnant woman of any gestation stage and therefore ADMA levels in any tissue or fluid sample cannot be relied as a marker for the diagnosis of IUGR or pre-eclampsia as set forth in the instant claims. It is apparent that ADMA is also regulated in other diseases such as obesity; fat intake, infection, cardiovascular disorder and thyroid function as supported by the cited arts. Therefore, because of the art, as shown above, does not disclose how a single marker such as ADMA could be a reliable biomarker considering the fact that many

other disorders also modulated the levels of ADMA. It is further noted that claim 1 only requires measurement of ADMA, but does not recite whether an increase or decrease of ADMA would indicate risk of pre-eclampsia. Thus, given that increased levels of ADMA are associated with various other conditions, measuring ADMA levels would not be sufficient to determine a pregnant woman's risk of developing pre-eclampsia or the fetus' rsik of developing IUGR. Furthermore, in a post filing art, López-Jaramillo (J Hypertens. 2005; 23(6): 1121-9 and references therein) while studying the role of ADMA in pre-eclampsia cite other references to indicate "that among 22 not pregnant, 22 normal pregnant and 22 pre-eclampsia Andean women, no difference in the plasma levels of ADMA was detected". López-Jaramillo further cite another recent report to that evaluated 160 Colombian women and found no differences in plasma ADMA concentrations among women with pre-eclampsia and women with normal pregnancy [0.43 (0.31–0.56) μmol/l versus 0.42 (0.29–0.55) μmol/l; $P = 0.42$; 95% CI for difference between the medians, -0.09 to 0.04]. It is noted that the study included different ethnic groups (White, African, Indigenous, and Multiethnic) and ADMA concentrations were no different from the white women who developed PE ($n = 12$) and those from the rest of the case group [0.44 (0.28–0.55) μmol/l versus 0.43 (0.32–0.61) μmol/l; $P = 0.83$; 95% CI for difference between the medians, -0.15 to 0.13]. López-Jaramillo concludes that that the etiologic process that leads to a vascular endothelial dysfunction are different between populations from developed and developing countries. While the immunological and genetic alterations are relevant in the development of pre-eclampsia in developed countries, nutritional, metabolic and infectious factors are the major responsible for the high incidence of pre-eclampsia seen in developing countries (see page 1126, col. 2, para. 3-5 and table 3). Thus, it is clear from the cited art that measuring the level of ADMA in a pregnant woman would not provide any reliable information as different etiological processes leads to a vascular endothelial dysfunction in different between populations and therefore instant

claims are not enabled. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).* It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994)*, citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991).* Artisan could not predict, in the absence of proof to the contrary, that such a method would be efficacious in the diagnosis of IUGR or pre-eclampsia. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because of the art of diagnosing pregnant woman predisposed of developing pre eclampsia or its fetus developing IUGR by measuring the levels of ADMA, a single biomarker is unpredictable and specification fails to provide any guidance as to how the claimed method would have been consistently practiced.

As a second issue, the scope of invention as claimed encompasses a method for of diagnosing whether a woman is predisposed of developing to pre-eclampsia or fetus susceptible to develop IUGR by measuring ADMA level in any tissue or biological fluid sample. The specification contemplates that the sample typically comprises a body fluid of the woman. The sample is preferably a blood, plasma, serum or urine sample but may be amniotic fluid (see page 5, line 30-31 of the specification). It is apparent that the reference or control used for comparison with the test level of the AMDA level may vary, depending on aspect of the invention being practiced. These values are subjective to sample population, other variables (age, gender, hormonal status, ethnicity, disease state), assay system and subjective to different interpretation by different artisan. In the instant case, specification has exemplified a method of measuring ADMA level in plasma sample. Recently, López-Jaramillo (J Hypertens. 2005; 23(6): 1121-9 and references therein) teaches that circulating ADMA may be secreted in different concentration depending on assay

system used to measure ADMA. This is further evident from different references level range described for normal or pre eclampsia pregnancy in the art (see table 3 and references therein). Claims as amended encompass comparing the level of ADMA in pregnant woman al with or without pre eclampsia or fetus with IUGR in any biological sample, it is relevant to point out the unpredictability with regard to the analysis of marker profiles obtained from different sample types. Cobb et al (2002) (Crit Care Med. 2002; 30(12):2711-21.) teaches the analysis of gene expression in spleen and liver sample from septic mice. Notably, the reference teaches that, when compared to a non-septic sample, the relevant biomarker profiles of the septic mouse spleen and the septic mouse liver contain different biomarkers (Table 1; page 2714, middle col. lines 2-8). It is thus unpredictable as to how one might use any reference marker profile comprising ADMA identified in a plasma in the analysis of a biomarker profile obtained from any other biological tissue or fluid sample. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in any pregnant women of any ethnicity suffering from multiple chronic disorders resulting in aberrant expression of ADMA level. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of identifying pre eclampsia in any pregnant woman by identifying the level of ADMA in plasma was not routine, rather it was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of identifying whether a woman is predisposed in developing pre eclampsia

or fetus susceptibility to IUGR such that it specifically correlate to aiding in the diagnosis of the disease. An artisan of skill would have required undue experimentation to practice the method as claimed because diagnosis of pre eclampsia by simply measuring the level of ADMA was unpredictable at the time of filing of this application as supported by the observations in the art record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the method does not recite a positive step linking the preamble to the claimed method it is unclear what method /process applicant is intending to encompass for the diagnosis of a woman developing pre-eclampsia or fetus at risk of developing IUGR. The impendent claim 1 merely recite measuring the level of ADMA level and dependent claim recite determining whether or not the level is 2.0 μmol/l without positive delineating what ADMA level of more or less than 2.0 μmol/l would actually mean to the method claimed. Claims 2, 4-11 directly or indirectly depend on claim 1. Appropriate correction is required.

Claims 2, 4-10 and 11 recite a limitation "according to" that simply requires to bring into agreement. Since, according only implies a level of agreement between two, thus metes and bound of instant claims are unclear. It is emphasized that more specific recitation of the claimed method such as " The method of claim.." would obviate this rejection. Appropriate correction is required. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Holden et al (Am J Obstet Gynecol. 1998; 178(3):551-6).

Claims are directed to a method of identifying whether or not a pregnant woman is at risk of developing pre-eclampsia or whether or not her fetus is at risk of developing intrauterine growth restriction (IUGR) by measuring asymmetric dimethylarginine (ADMA) in the pregnant woman (4-25 weeks gestation) and determining whether or not the ADMA level is greater than 2.0 □mol/L. As recited these claims do not require any specific level that is more or less than 2.0 μmol/L for the diagnosis of the pre-eclampsia, therefore in absence of any specific level of ADMA, determining whether or not woman is at risk of developing pre-eclampsla or determining her fetus is at risk of developing IUGR is not given any patentable weight (also see 112, paragraph 2 rejection , supra.

Holden et al teach measuring plasma asymmetric dimethylarginine (ADMA) level in 145 pregnant women that included pregnancy of all stages (first to third – trimester). It is noted that Holden et al also determined the level of ADMA which varied from 0.52 μmol/L to 1.17 μmol/L depending upon stage of pregnancy . This would meet the claim limitation of different stage of pregnancy (4-25, 10-25 or 15-25 weeks) that is embraced by the teaching of Holden (see page 553, Figure 1 B). It isnoted that Holden et al conclude that during later stage of pregnancy circulating

concentrations increase and, when pregnancy is complicated by preeclampsia. Thus, method of Holden is primarily directed to study the role for asymmetric dimethylarginine in the changes in blood pressure seen in both normal and preeclamptic pregnancy (see abstract and page 555, col. 1, para. 4).

Accordingly, Holden et al anticipate claims 1-2, 4 and 5.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Kisters et al J Hypertens. 2006 Jan;24(1):201; author reply 202. Fickling et al (Lancet., 1993, 342, 242-243).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the

Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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